REMARKS

Upon entry of the present amendment, claims 1-8 and 13-18 are pending in the instant application. Of these, claims 1-6, 8, and 14-18 have been withdrawn from consideration subject to the restriction requirement of September 17, 2007. In an effort to expedite prosecution, Applicants have amended elected claims 7 and 13 to clearly specify that the mosaic Phl p 2 allergen and associated vaccine of the instant invention is "hypoallergenic", "having reduced allergenic activity as compared to Phl p 2 wild type". Support for this amendment is found in the as-filed specification, for example at p. 1, lines 1-5, p. 3, lines 1-4, and pp. 11-12 (Example 3). However, Applicants reiterate that this amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Pursuant to the Non-Final Office Action of January 10, 2008, elected claims 7 and 13 stand rejected on non-reference grounds only, namely failing to comply with the enablement and written description requirements under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that the instant response renders moot the outstanding claim rejections and places the instant application in condition for allowance. Further to this position, Applicants submit the following remarks:

Rejections Under 35 USC 112, First Paragraph

Enablement:

Claims 7 and 13 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. According to the Examiner, while the specification is enabling for a mosaic allergen consisting of SEQ ID NO: 1, it does not reasonably provide enablement for: (a) a mosaic allergen having the amino acid sequence of SEQ ID NO: 1 or (b) a vaccine for the treatment of allergic patients characterized as comprising a mosaic allergen having the amino acid sequence of SEQ ID NO: 1.

With respect to issue (a), the Examiner asserts that the specification does not provide sufficient support for a mosaic allergen "having" the sequence of SEQ ID NO:1, noting that the

term "having" is open-ended and broadens the claim to encompass many more peptides than the specification provides enablement for, with unlimited amino acids added to the N- and/or C-terminals of the peptide. According to the Examiner, such undisclosed amino acids may function to treat allergies independent of the SEQ ID NO: 1.

It is important to note that specification is presumed to be in compliance with the enablement requirement of 112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. For an Examiner to sustain a rejection on the grounds of enablement, she must provide evidence that the claimed method could not be performed without undue experimentation, bearing in mind that the test for undue experimentation is not merely quantitative. In fact, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. There are many factors to be considered when determining whether the specification is enabled and whether any necessary experimentation is "undue". They include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention.

In this case, the instant specification clearly contemplates N- and C-additions, noting that "it is also possible to link the mosaic allergen directly by covalent bonding to another component which generally enhances the immunologic reaction of the body." See p. 6, lines 4-7. However, it seems that the Examiner is of the opinion that general guidance is not sufficient, that without specific guidance as to which amino acids may be added to the N- and/or C- termini of SEQ ID NO: 1, the experimentation left to those skilled in the art is undue. Applicants respectfully disagree. Given the high level of skill in the art and the fact that a vast number of adjuvant and fusion constructs are presently known and indeed conventional in the art of peptide-based immunotherapy, the "trial and error" testing needed to identify suitable N-terminal or C-terminal additions is within

the parameters of routine experimentation and optimization. Furthermore, while it is well settled that the presence of some potentially inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled (see *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)), Applicants respectfully submit that such potentially inoperative embodiments are excluded by the current claim language (e.g., a "hypoallergenic mosaic allergen…having reduced allergenic activity as compared to Phl p 2 wild type"), which requires that the sequence at issue display reduced allergenic activity, i.e., reduced IgE reactivity binding capacity, reduced induction of basophil histamine release, reduced wheal reaction, as compared to the wild type Phl p 2 grass pollen allergen. Thus, in that a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the presently pending claims without undue experimentation with a reasonable expectation of success.

With respect to issue (b) and the enablement of the vaccine of claim 13, the Examiner asserts that, given the absence of specific and detailed description in the specification as to how to effectively use the vaccine as claimed, given the absence of working examples providing evidence which is reasonably predictive of *in vivo* efficacy in the treatment of allergy, given the lack of predictability in the art at the time of invention, and given the fact that a vaccine composition must be able to induce specific immunity that prevents or protects against a specific disease caused by a specific agent, an undue amount of experimentation would be required to practice the claimed vaccine with a reasonable expectation of success.

At the outset, Applicants takes issue with the Examiner's suggestion that the term "vaccine" implies 100% prevention ("[While the] invention may reduce the likelihood of allergy by administering a mosaic allergen having the amino acid sequence of SEQ ID NO: 1. . .the specification does not disclose <u>how to totally prevent</u> allergy." – emphasis added). As citations from dictionary.com and wikipedia.com, provided herewith as Appendices A and B, respectively, demonstrate, the art-recognized definition for the term "vaccine" is a preparation used to <u>*improve immunity*</u> to a particular disease, one that, upon administration <u>*stimulates antibody production or*</u>

cellular immunity against the pathogen but is incapable of causing severe infection. Furthermore, it is well settled that vaccines can be both prophylactic (e.g. preventing or ameliorating the effects of a future infection), or therapeutic (e.g. inducing a therapeutically effective immune response against a present disease condition). Thus, Applicants respectfully submit that the term "vaccine", when afforded its ordinary and customary meaning, does not necessarily equate to 100% prevention. Moreover, Applicants respectfully submit that one skilled in the art would readily recognize that, in the context of the instant claims, the term "vaccine" encompasses a wide range of prophylactic therapies aimed at alleviating the onset or severity of one or more allergic symptoms. Accordingly, Applicants need not disclose "how to totally prevent allergy" to enable the invention of the pending claims.

Furthermore, regarding the "how to use" prong of 35 U.S.C. § 112, first paragraph, it is important to note that the statute does not require a specification to enable all uses of the claimed invention; rather, a single disclosed or well-established use will suffice. See M.P.E.P 2164.01 (c): "If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." As discussed previously and in greater detail below, Applicants respectfully submit that they have met this burden.

The Examiner states that the first criterion in judging a vaccine is the level of antibody (humoral immune response) before and after immunization, wherein the success of the vaccine is judged by the extent of increase in the level of antigen-specific antibody. The second criterion for a vaccine is its ability to stimulate memory T lymphocytes. The Examiner thus concludes that since, "vaccines by definition trigger an immunoprotective response in the host vaccinated", "mere antigenic response is insufficient". The Examiner goes on to suggest that substantiating evidence of enablement in the form of animal tests or other assays which constitute recognized screening procedures with clear relevance to efficacy in humans may be useful in demonstrating the alleged therapeutic utility of the vaccine of claim 13.

To that end, Applicants submit herewith as Appendix C an in-press manuscript by the

present inventors entitled "Disruption of Allergenic Activity of the Major Grass Pollen Allergen Phl p 2 by Reassembly as a Mosaic Protein". Therein described is the mosaic allergen of the instant invention, an allergen that has lost the three-dimensional structure, IgE reactivity and allergenic activity of the wild-type Phl p 2 grass pollen allergen yet can induce high levels of allergen specific IgG antibodies upon immunization, such IgG antibodies capable of cross-reacting with group 2 allergens from other grass species and inhibiting allergic patients' IgE binding to the wild-type allergen. In particular, Applicants direct the Examiner's attention to pp. 17-18, which describe the immunization of rabbits with the Phl p 2-derived mosaic allergen of SEQ ID NO: 1 and the subsequent induction of high levels of Phl p 2-specific IgG antibodies as compared to immunization with recombinant wild-type Phl p 2. Accordingly, Applicants submit that the Examiner's first criterion has been met. As for the Examiner's second criterion, Applicants direct the Examiner's attention to p. 19, lines 3-10, wherein the ability of the Phl p 2-specific IgG antibodies induced by immunization with the Phl p 2-derived mosaic allergen of SEQ ID NO: 1 to inhibit IgE binding of grass pollen allergic patients to rPhl p 2 is described. These so-called blocking antibodies substantially prevent contact between the allergen and the IgE molecules present in the allergic patient's body, thereby avoiding mast cell- and basophil-mediated allergic responses, such as cytokine secretion and histamine release. Thus, it is readily apparent that the vaccines of the instant invention are capable of generating an "immunoprotective" response in the host vaccinated.

In sum, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification as well as the attached manuscript demonstrate that a reasonable correlation exists between the scope of the claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the presently pending claims without undue experimentation with a reasonable expectation of success.

Therefore, Applicants respectfully request reconsideration and withdrawal of the enablement rejection of claims 7 and 13 in view of the amendments and remarks herein.

Written Description:

Claims 7 and 13 stand rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to reasonably convey possession of the claimed invention. Specifically, while the Examiner accedes to Applicants' possession of a mosaic allergen consisting of SEQ ID NO:1, she challenges whether Applicants were in possession of (a) a mosaic allergen having the amino acid sequence shown in SEQ ID NO: 1 or (b) a vaccine comprising such a mosaic allergen, having the amino acid sequence shown in SEQ ID NO: 1

The standard for determining compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). The standard for determining sufficiency of the description is "factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *In re Wertheim*, 541 F.2d at 262 (citing *In re Ruschig* 379 F.2d 990, 995-96 (C.C.P.A. 1967)). It is well accepted that a specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that the claim encompasses. The law does not require that the specification describe the exact details for preparing each and every species within the genus described. In fact, even if the Examiner considers the subject matter of the claims to be broader than that disclosed in the original specification, the written description requirement may be satisfied if the broader concept would naturally occur to one skilled in the art upon reading the earlier specification.

In this case, Applicants respectfully disagree with the Examiner's position and submit her conclusions are in conflict with the recently promulgated Revision 1 of the Written Description Training Materials published March 25, 2008 (www.uspto.gov/web/menu/written.pdf), particularly Examples 4 and 15, both of which validate the use of open-language in this context. In assessing adequacy of written description, the examples expressly conclude that it is within the level of skill and knowledge in the art to add any desired DNA sequence to either end of a particular sequence, with no more than routine experimentation. Because the claimed sequence is a structural feature

common to members of the claimed genus and the specification describes the complete structure (sequence) of the molecule, one skilled in the art would recognize that the applicant was in possession of a structural feature shared by members of the claimed genus. Accordingly, a single species in the specification; *i.e.,* SEQ ID NO: 1, is sufficiently representative of the claimed genus and thus the written description requirement of 35 U.S.C. 112, first paragraph, is satisfied.

Thus, Applicants respectfully submit that the instant specification provides an adequate written description of the genus of mosaic allergens encompassed by claims 7 and 13, so as to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention now claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejection of claims 7 and 13 in view of the amendments and remarks herein.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **April 10, 2008**. In that the Petition for a Three-Month Extension of Time extends this deadline to on or before **July 10, 2008**, Applicants respectfully submit that this response is timely and no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, he is invited to contact the undersigned.

Respectfully submitted,

Date: /July 8, 2008/

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Attachments:

- Appendix A: Vaccine Citations from Dictionary.com;
- Appendix B: Vaccine Citation from Wikipedia.com;
- Appendix C: In-Draft Manuscript of Nadine Mothes-Luksch et al.